The Environment as an Etiologic Factor in Autism: A New Direction for Research

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Autism is one of a group of developmental disorders that have devastating lifelong effects on its victims. Despite the severity of the disease and the fact that it is relatively common (15 in 10,000), there is still little understanding of its etiology. Although believed to be highly genetic, no abnormal genes have been found. Recent findings in autism and in related disorders point to the possibility that the disease is caused by a gene–environment interaction. Epidemiologic studies indicate that the number of cases of autism is increasing dramatically each year. It is not clear whether this is due to a real increase in the disease or whether this is an artifact of ascertainment. A new theory regarding the etiology of autism suggests that it may be a disease of very early fetal development (approximately day 20–24 of gestation). This theory has initiated new lines of investigation into developmental genes. Environmental exposures during pregnancy could cause or contribute to autism based on the neurobiology of these genes. *Key words*: autism, autism epidemiology, autism etiology, children, developmental disorders, retinoids, gene–environment interaction, *Hox* genes. — *Environ Health Perspect* 108(suppl 3):401–404 (2000).
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The autism spectrum disorders (otherwise known as the pervasive developmental disorders) include autistic disorder as well as pervasive developmental disorder not otherwise specified and Asperger's syndrome. These three are all widely believed to be developmental brain disorders. It is quite likely that there are environmental factors that contribute to the brain pathology which yields the symptoms found in autism.

Diagnostically, the autism spectrum disorders are highlighted by a triad of symptoms. These include language disturbance, social impairment, and a rigid adherence to sameness (*1,2*). There is a spectrum of severity of these symptoms ranging from being "almost normal" to completely nonfunctioning. The language disturbance ranges from "odd" to totally nonverbal. At the severe end of the spectrum, the disease takes an enormous toll on both the affected individual and the family. Often the family is drawn into a lifelong care-taking role and family members may abandon much of what may be considered a normal healthy life. One study (*3*) concluded that the amount of family stress was significantly higher in families with an autistic family member than in families affected by a fatal disease like cystic fibrosis.

Conservatively, autism spectrum disorders affect over 400,000 people in the United States (*4,5*). Although autism is one of the most severe in terms of morbidity, other developmental brain disorders are far more prevalent. There are an estimated 7 million individuals with mental retardation in America (*6*). At the other end of the spectrum of developmental brain disorders, Attention Deficit Disorder and learning disabilities are each estimated to occur in up to 10% of the population (*7*). This would bring the total population of people with developmental brain disorders in the United States to over 20 million individuals. Except for a few types of mental retardation such as Down's syndrome and Fragile X syndrome, the etiology of the developmental brain disorders is unknown. The most common etiology of mental retardation is "mental retardation of unknown origin."

Environmental factors can cause developmental disabilities. Obvious examples are fetal alcohol syndrome and phenylketonuria (considering phenylalanine as the environmental agent). Despite the severity and prevalence of this group of diseases, and with the likelihood that environmental influences are at least partially responsible, there has been little research in this field. Weiss (*8*), in a review of pesticides as causes of developmental disorders, pointed out that our knowledge of how those agents modify the course of brain development is "disturbingly sparse," and offers four areas of deficiency in our knowledge. These areas are *a*) a lack of epidemiologic studies based on developmental exposure; *b*) a lack of animal models addressing development, including wide dosing ranges to simulate environmental realities; *c*) the fact that animal studies use crude behavioral end points rather than more sophisticated ones such as intellectual development; and *d*) the fact that longitudinal lifetime experiments are rarely aimed at neurobehavioral end points (therefore preempting the study of symptoms emerging later in life). For example, autism is not usually diagnosed until approximately 18 months of age despite evidence of prenatal changes in the brain. Weiss' observations could be generalized to include all environmental research on the developmental disorders rather than just research on pesticides.

We describe the current state of environmental research in autism to illustrate the issues faced by those interested in pursuing the etiology of developmental brain disorders. Because this work is in its infancy, we include not only the existing research but also some of the newer hypotheses. We believe that investigating environmental factors in the etiology of autism will be a fruitful avenue to pursue.

Autism and the Interaction of Genes and Environment

Although the etiology of autism is not understood, there is clearly a genetic component to autism spectrum disorders (*9,10*). This has been established through twin and family studies. There is a concordance rate of approximately 2–6% in dizygotic twins as opposed to the 66% concordance rate in monozygotic twins. This 2–6% rate is also the rate estimated for family recurrence, which should be compared to the approximate rate of 0.1–0.15% in the general population. Despite the evidence of a genetic component, however, genetics does not explain the whole picture (*1,9*). Autism is most likely a "multifactorial" disorder. Wide-ranging phenotypes, both within families as well as within the monozygotic twins studied, suggest that simple modes of inheritance are not operative. Furthermore, case reports of autism associated with environmental factors, such as rubella virus, valproic acid, and thalidomide exposure during pregnancy, lead many researchers to postulate that nongenetic mechanisms may also produce an autistic syndrome.

Virtually all of the psychiatric disorders appear to be syndromes genetically comprised of complex traits. Psychiatric diagnoses based on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (American Psychiatric Association, Washington, DC) are phenomenologic and not etiologically based. This simple but often overlooked fact has a profound effect on the search for etiologies.

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Another way of stating the above is that psychiatric diagnoses are merely statistically based groupings of symptoms. Along with the formal diagnosis of autistic disorder, there is wide acceptance of an entity known as the broader autistic phenotype. The meaning of the broader phenotype is that autistic traits such as language disturbance, social disturbance, and learning disorders are significantly more common in the families of autistic probands (*11–13*). For example, although the concordance for autism in identical twins is approximately 66%, it is about 93% for the broader phenotype (*14*). Similarly, the rate in dizygotic twins for concordance for the broader phenotype is approximately 15% rather than 2–6%. The understanding that affected family members may have some of the genetic makeup of autism without having the disease has led many investigators to postulate the concept of susceptibility genes for autism. If this is the case, perhaps it would be necessary to have both these susceptibility genes as well as some environmental regulation of these genes to produce autism.

Like most of the psychiatric illnesses, autism appears to be a syndrome of complex genetic traits (*15*). These traits are phenotypes that do not exhibit classic Mendelian recessive or dominant inheritance attributable to a single gene locus. This can happen either because different genotypes can result in the same phenotype or because the same genotype can result in multiple phenotypes. The latter can be the result of genetic interactions with the environment or with other genes.

A gene associated with Rett's syndrome was recently identified (*16*). This is believed to be the first gene associated with a specific disease that has a role in the epigenetic regulation of gene expression and is therefore a gene which could explain the clinical appearance of these complex traits. It should be noted that this mutation was found in approximately 30% of those studied. Although regulatory genes are an exciting prospect for the explanation of complex genetic illnesses, the environmental regulatory role should not be considered less significant. The research on psychiatric illnesses has not identified abnormal genes. This led Kandel (*17*) to muse that "certain combinations of normal genes against a certain genetic background ... may predispose people to getting schizophrenia. And if the latter is the case, then finding any gene by itself may not be helpful because it may be a normal gene." If this turns out to be the situation in autism, then studying the expression of the genes (and their regulators) may give us more clues to understanding its etiology.

Genes have two roles: the template function (replication) and the transcriptional function (which is responsible for the structure, function, and other biological characteristics of the cell). In this process, the DNA codes for and creates the RNA, which then goes on to code for and create the proteins. Although the template function is largely independent of outside forces, the transcriptional function is highly regulated and responsive to environmental factors (*18*). These environmental factors could be toxicants, viruses, or hormones. As an everyday example, the process of learning has a direct effect on an organism's genes and their functioning. Environmental stimuli guide the neurons to grow, synapse, or perhaps die according to what is needed. If even the physiologic interaction with the environment alters genetic functioning, the role of outside toxicants or of disturbed metabolism due to toxicants can also have the same result. Although there is evidence that exposure to a distinct environmental factor during pregnancy (i.e., infection with Rubella virus) can cause an autistic syndrome, the most likely avenue for fertile research will be in the gene–environment interaction.

Epidemiology of Autism

Is the prevalence of autism increasing? Throughout the 1960s and 1970s the prevalence of autism was believed to be 2–5 in 10,000. Nearly all of the epidemiologic studies done before 1985 reflected findings in that range (*5*). Since 1985, however, 10 of 11 studies done outside of the United States showed rates of 9 per 10,000 or more. There have also been some studies, the most detailed with respect to case-finding, that showed rates of > 20 per 10,000. However, these studies were performed on small populations. One group performed repeated studies in the same geographic area in Goteborg, Sweden (*5*). In 1980 they reported a prevalence of 4 per 10,000; in 1984 prevalence was 7.6 per 10,000, and in 1988 prevalence was 11.5 per 10,000. Gillberg and Wing (*5*) estimated that based on worldwide epidemiologic studies autism appears to be increasing at a rate of 3.8% per year. It is not clear whether the apparent rise in prevalence is a real increase or a function of better ascertainment.

In April 1999, the state of California reported an increase of 210% in the autism population receiving services through its regional centers (*19*). Regional centers are those state-supported institutions with responsibility for providing services to the developmentally disabled population. It is likely that most families with developmental disabilities would utilize these resources, so it is probably a good representation of the relative prevalence of autism. The 210% rise in autism is compared to an approximately 60% increase in total population that the regional centers served between 1987 and 1998. Although the report emphasized that this is not an epidemiologic study, the extreme increase in numbers is striking and has led the state of California to study autism further.

The Brick Township Cluster

Brick Township, New Jersey, is a rural township close to several Superfund sites. The number of autistic children in the township, combined with existing concerns over environmental issues, led a group of parents in the township to begin informal surveillance for autism. They placed ads in local newspapers asking for parents of autistic children to identify themselves. Many individuals responded, which, if confirmed, would indicate that the prevalence of autism in Brick Township was much higher than the usually cited prevalence. These observations led the Centers for Disease Control and Prevention (CDC) (Atlanta, GA) and the Agency for Toxic Substances and Disease Registry (ATSDR) (Atlanta, GA) to conduct an investigation. On 22 May 2000, the reports of both agencies were made public. The CDC, using the Autism Diagnostic Observation Schedule-Generic to confirm diagnoses, found that the prevalence for strictly defined autism was 4 per 1,000 and that the prevalence for strictly defined autism was 6.7 per 1,000 (*20*). These prevalence figures are approximately 4 times higher than the 1 per 1,000 most frequently cited in the literature. The ATSDR studied the township environmentally and found three contaminants in the drinking water at various times (*21*). These substances were tetrachloroethylene, trichloroethylene, and trihalomethanes (THMs). In all three cases there was no evidence of a link between the location and/or timing of the abnormal values and the indexed cases of autism. The most interesting finding, however, is that THMs within the same range as found in Brick Township have been associated with a 2-fold increase in neural tube defects (*22,23*). This finding should be considered in the context of Rodier's research (*24*), which hypothesizes that autism may be caused by a neural tube defect.

Because of the lack of surveillance, we do not know the prevalence of autism worldwide or in the United States. Nor do we know if the prevalence is uniform in its distribution or higher in some geographic areas than others. It is not clear whether the disease is rising in prevalence. In 1995, the working group on epidemiology of the National Institutes of Health (NIH) autism committee concluded that there was no need for undertaking further epidemiology study in the United States (*25*). In the last year, however, the NIH indicated a renewed interest in autism epidemiology in its call for proposals. To study environmental causes of autism and to understand its prevalence, rate of increase, and geographic clustering are crucial.

The Neurobiology of Autism

Much of what we can deduce about the etiology of autism comes from two neuropathologic studies of postmortem samples (*26,27*). Evidence that there are limbic system abnormalities is based both on neuropathological findings as well as neuropsychological theory (*28*). New research on cognitive brain mechanisms point to cerebellar malfunctioning as a central explanation for many of the signs and symptoms of autism, including the cognitive deficits (*29*). This is underscored by neuropathological and neuroimaging findings that point to the cerebellum as being abnormal. Although there are some inconsistent findings, there also have been some findings found uniformly in all postmortem tissue examined. In all of the brains studied, Purkinje cell numbers were diminished without the presence of empty baskets. This suggests that it is unlikely that these cells were lost but rather that there was a very early developmental abnormality. Evidence of abnormal neuronal migration appears to be present in the brain stem, cerebellum, and the cortex. These abnormalities indicate that the brain lesions in autism occurred very early in fetal development. Although we cannot rule out the possibility that there are insults to the brain postnatally, any explanation of the etiology will have to explain these early developmental brain changes. Therefore, for those who are interested in investigating possible environmental causes of autism, the *in utero* period is a crucial time to study (*26,27,30*).

There is not a good animal model for autism. A disease that is characterized by language and social impairment is hard to demonstrate or test in animals. Nevertheless, this is an area of high priority and recently led the NIH to sponsor a conference on animal models in autism. The conference, Building Animal Models for Autism Through Translational Neuroscience Research, held 5–6 October 1998 in Santa Monica, California, generated several new strategies for the development of an animal model. Even with an animal model, assessing the effects of various toxicants is difficult. Wide ranges of doses and varied exposure times must be studied. The developmental aspect of the brain in terms of the effect of a toxicant is especially important. Better behavioral measures will also be needed to determine the effects that these substances have on the developing brain.

Autism as a Birth Defect

On 10–11 April 1995 the NIH held the Autism State-of-the-Science Conference in Bethesda, Maryland. Genetics research was reviewed, but scant attention was given to any other etiologic hypotheses. At that time, there was no literature to support any environmental factor or even an environmental hypothesis. However, at approximately the same time, a group of ophthalmologists was studying the Swedish thalidomide survivor population (*31*). Eighty-six people who had been exposed to thalidomide *in utero* were examined for ocular motor defects. In this group, 15 patients with early exposure to the drug had external ear malformations but no limb abnormalities. This would suggest that they were exposed to the thalidomide between days 20 and 24 of gestation. Of the 86 there were 4 who were autistic. All 4 patients were among the 15 who had the early exposure to thalidomide; no cases of autism were found outside of that window of exposure.

The hypothesis that autism could be caused by a disturbance of neural tube closure was formulated by Rodier (*24*) based on this research. The neural tube closure process occurs during the gestation day 20–24 timeframe. This was a breakthrough in thinking about the etiology of autism and could be described as the first evidence-based etiologic hypothesis of autism. To further explore this theory, Rodier et al. (*32*) have pursued several lines of investigation. Examination of some postmortem tissue has shown abnormalities in the brainstem structures also formed during that same time period. Elevated levels of cranial nerve abnormalities have been reported; however, because of their relatively minor clinical importance, they have been somewhat overlooked. A rat model has been produced by using valproic acid (another interrupter of neural tube closure), which yielded reductions in the numbers of neurons in cranial nerve nuclei as well as malformed ears. Rodier et al. (*32*) also noted a decrease in the number of Purkinje cells in the cerebellum. These findings are similar to those reported in the postmortem studies of individuals with autism (*26,27*).

These findings led researchers to explore the possibility of a candidate gene being etiologically involved in autism. The genes come from the family known as the *Hox* genes. This family comprises 38 different genes and is expressed during embryonic development. They pattern for many body structures, including the limbs, skeleton, and the nervous system. There is literature to support the fact that knockout mice lacking *Hoxa1* and *Hoxb1* have some of the same abnormalities as the valproate rat as well as the clinical cases of autism. This suggests that the abnormality in development in autism might be mediated through these genes. Preliminary work from this group suggests that allelic variants of *HOXA1* occur at a higher rate among autistic probands than in several control groups. Another interesting finding is that these variant alleles were not rare in the control populations (*33*).

If these findings are correct, this would have a major impact on the relevance of environmental exposures to the etiology of autism. It suggests that the genes responsible for autism might be thought of as susceptibility genes. Perhaps the genes mediate only the broader phenotype (which appears to be even more heredible). To have the full autistic syndrome we might need the genetic predisposition as well as some other event or exposure, most likely *in utero*. The *HOXA1* findings raise the possibility that, with a candidate gene identified, the task of finding environmental exposures that contribute to autism is at hand.

Retinoid Research

The theory that autism is caused by an abnormality in development at the time of neural tube closure has opened the door to looking at retinoic acid as a possible environmental factor. Converging lines of evidence make looking at this compound compelling.

The retinoids can be powerful teratogens. The study of this topic is, however, quite complicated. One major finding that complicates the picture is that the effects of the retinoids (as well as other toxicants that interrupt neural tube closure) are species dependent. Thalidomide, for example, can produce limb malformations in humans and most subhuman primates. The defects can be produced in rabbits at high doses, but rats and mice are not susceptible. Three albino rat strains differ in their responses to excess vitamin A. Dosing and timing of the retinoid exposure also yield very different results (*34*).

Both an excess and a deficiency of vitamin A during pregnancy are associated with birth defects, specifically neural tube defects [the same type of damage postulated by Rodier to occur in autism (*24*)] (*35*). In 1995, the Food and Drug Administration issued new recommendations warning women in their childbearing years to limit their Vitamin A intake to 5,000 IU (*36*).

In a survey of 22,000 women, Rothman et al. (*37*) reported much higher rates of birth defects in those women who took excessive doses of vitamin A during pregnancy. This study has been criticized by several authors (*38*). Mastroiacovo et al. (*39*) did not find the same correlation between high levels of vitamin A and birth defects. From the point of view of autism research, however, the fact is that in both studies the data were collected shortly after the delivery of the baby. Because of this, neither study would have been able to identify any cases of autism, as autism usually presents around the second year of life. In addition, the studies would not have been able to identify more subtle abnormalities of cognition that may need to be measured in early childhood.

Besides Vitamin A, there are other forms of retinoids to which women may be exposed during pregnancy. There are several retinoid-based medications, including isotretinoin, an acne medication. Isotretinoin causes birth defects including hindbrain abnormalities that resemble the brain abnormalities in autism (*40*). The evidence that retinoids are capable of being teratogens is of importance because these compounds are used in treatment of skin diseases as well as in cancer treatments. To date, there have been more than 10,000 retinoids isolated or synthesized for potential pharmacological application (*34*).

Animal models using retinoic acid have been developed and share many of the specific brain lesions associated with autism including cerebellar malformations, cranial nerve abnormalities, and abnormalities of the dopaminergic system.

Retinoids may also be direct environmental pollutants, although this may not be the mechanism by which this group of compounds influences brain development in autism. It is likely that other forms of toxicants may interfere with retinoid metabolism. Various chemicals (such as polychlorinated biphenyls) and hormones (such as thyroid hormones) can alter retinoid metabolism (*41*). Valproic acid, which is believed to be a possible etiologic agent for autism, also alters retinoid metabolism (*42*).

Perhaps the most interesting nexus between the retinoids and autism is the fact that they are known modifiers of *Hox* genes (*35*). It is quite possible that the findings of birth defects caused by retinoids are mediated through their properties as genetic modifiers.

The Case for Environmental Research in Autism

At this point the evidence for an environmental origin for autism is circumstantial. Direct evidence for any etiology in autism is thus far lacking. Nevertheless, we contend that there are ample reasons for environmental research to be undertaken.

Although autism is a highly heritable disease, no genes or even areas of interest have emerged as highly significant. Rather than continuing to search for abnormal genes, a more productive strategy may be to study the expression of the genes. New techniques such as the use of microarrays enable the direct examination of gene expression in brain tissue. The wide phenotypic variation even in some identical twins further points to gene expression rather than just genotypic abnormalities as part of the etiologic mechanism. Studies of the regulator genes as well as environmental regulators can be looked at as a fruitful strategy. Environmentally induced animal or even tissue models may help to identify candidate genes.

The embryologic origins of autism further give a direction for investigators. The neurobiology of the prenatal developmental processes, and the environmental exposures that can effectuate those changes, may be a clue leading to an understanding of the origins of autism. An example might be dysmorphic facial and body features. The fact that environmental factors (such as retinoids) can produce these changes in the same children who have diseases such as autism might lead us toward the mechanisms of abnormal brain formation.

Studies such as the Brick Township surveillance, yielding either an increased prevalence or geographic clustering, would further open the possibilities that an environmental factor could be found. This study has a component to look for environmental factors that may be linked to autism.

We have attempted to outline some of the emerging concepts in understanding the etiology of autism. To advance the research, various lines of investigation must be pursued, including identifying genetic abnormalities and studying the basic neurobiology of the disease. Epidemiologic studies of autism should be undertaken. The environmental scientist has a great deal to contribute to the understanding of autism and other developmental brain diseases.

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